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Routinely measured iohexol GFR versus creatinine based eGFR as predictors of mortality in patients with advanced CKD: a Swedish CKD Registry cohort study

Running title: mGFR vs eGFR to predict mortality in CKD

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Summary

How we measure excretory renal function is a core component of clinical nephrology encountered daily in clinics around the world, but there is still uncertainty about the optimal measurement for patients with advanced kidney disease (when eGFR prediction equations are less reliable). This cohort study from the Swedish CKD Registry compares routinely collected plasma-iohexol measured GFR or 24-hr urine clearances with eGFR to predict mortality in a large number of Swedish patients with Stage 4/5 CKD. We found that mGFR has a statistically superior performance to eGFR in both aetiological and prognostic models, demonstrating the importance of GFR per se versus non-GFR determinants of outcome. However, the relatively modest enhancement suggests that eGFR may be sufficient to use in everyday clinical practice while mGFR adds important prognostic information for those where eGFR is believed to be biased.

Abstract

Background

Estimated GFR (eGFR) becomes less reliable in patients with advanced chronic kidney disease (CKD).

Methods

Using the Swedish CKD Registry (2005-2011), linked to the national inpatient, dialysis and death registers, we compared the performance of plasma-iohexol measured GFR (mGFR) and urinary clearance measures versus eGFR to predict death in adults with CKD Stages 4/5. Performance was assessed using survival, and prognostic models.

Results

Of 2705 patients, 1517 had mGFR performed, with the remainder providing 24-hr urine clearances. Median eGFR (CKD-EPI$_{creatinine}$) was 20ml/min/1.73m^2 (interquartile range [IQR] 14–26), mGFR 18ml/min/1.73m^2 (IQR 13–23) and creatinine clearance 23ml/min (IQR 15-31). Median follow-up was 45 months (IQR 26-59), registering 968 deaths (36%). In fully-adjusted Cox models, a rise in mGFR of 1ml/min/1.73m^2 was associated with a 5.3% fall in all-cause mortality compared with a 1.7% corresponding fall for eGFR (adjusted hazard ratio [aHR] 0.947 [95%CI 0.930–0.964] versus aHR 0.983 [95%CI 0.970–0.996]). mGFR was also statistically superior in prognostic models (discrimination using logistic regression and integrated discrimination improvement). Urinary clearance measures showed a stronger aetiological relationship with death than eGFR but were not statistically superior in the prognostic models.

Conclusions

The performance of mGFR was superior to eGFR, in both aetiological and prognostic models, in predicting mortality in adults with CKD stage 4/5, demonstrating the importance of GFR per se versus non-GFR determinants of outcome. However, the relatively modest enhancement suggests that eGFR may be sufficient to use in everyday clinical practice while mGFR adds important prognostic information for those where eGFR is believed to be biased.

Introduction

Chronic kidney disease (CKD) is associated with adverse patient outcomes(1). Identifying reduced glomerular filtration rate (GFR) is key for the classification of kidney disease and prognostication for patients with CKD(2). GFR is approximated by measuring plasma clearance of an exogenous substance such as iohexol (measured GFR [mGFR]) or measuring an endogenous marker, such as creatinine. Estimated GFR (eGFR) is derived from the serum creatinine concentration, adjusted for creatinine generation on the basis of age, sex and race. Urinary creatinine excretion can be measured directly using a timed urine collection (usually 24 hours) and calculating the creatinine clearance (Creat-Cl)(3).

Creatinine based eGFR is subject to inaccuracy; eGFR over-estimates true GFR in people with low muscle mass (reduced creatinine generation), including those with advanced kidney or liver disease(4-6) and underestimates GFR in case of high muscle mass. However urinary creatinine excretion, which is a measure for muscle mass, is also an independent prognostic marker; low creatinine excretion is associated with increased all-cause mortality(7). These associated observations affect the utility of creatinine based eGFR both as a measure of excretory kidney function (due to inaccuracy), and as a prognostic marker for increased mortality. This is because the relationship between eGFR and adverse outcomes is confounded by creatinine generation. Creatinine generation is a key non-GFR determinant of outcome. Whether accurate measure of kidney function or prognostic ability should take precedence in our choice of filtration marker is debated(8, 9).

In Sweden, many patients with advanced CKD routinely have formal GFR measurement (mGFR or urinary urea/creatinine clearance) along with eGFR. To assess the contribution of GFR and non-GFR determinants to patient outcome, we compared the performance of eGFR with measured GFR to predict all-cause mortality in patients registered with the Swedish Renal Registry – Chronic Kidney Disease (SRR-CKD).

Subjects and Methods

Study population

SRR-CKD prospectively collects data for all patients attending 49 of 51 nephrology clinics in Sweden (2014) with incident eGFR<45ml/min/1.73m^2(10). GFR measurements (iohexol mGFR or urinary clearances of urea, creatinine or urea-creatinine) are performed routinely in most Swedish nephrology clinics, but there is no uniform protocol. This study included patients ≥18 years who had *either* an iohexol mGFR *and/or* urinary clearance (creatinine clearance [Creat-Cl], urea clearance [Urea-Cl] or urea-creatinine clearance [Urea-Creat-Cl]) *and* a serum creatinine measurement between 1st January 2005 and 31st December 2011, on the day of a nephrology clinic visit (for contemporaneous clinical measures). Data linkage with the Swedish Inpatient Register provided co-morbidity data (ICD-10 codes from 1987 onwards), to calculate Charlson scores(11). We linked with the SRR and the Cause of Death Registry for date of renal replacement therapy (RRT) (including pre-emptive transplantation) and vital status until 30th Sept 2013. Duplicates were removed, then patients were excluded (criteria shown in Figure 1). Outlier GFR results were removed on the assumption that the result was not biologically plausible (when the absolute difference between mGFR and eGFR was >3 standard deviations from the mean absolute population difference). Primary renal diagnosis (PRD) was reported according to the European Renal Association codes(12).

Laboratory measurements

Iohexol is an iodinated contrast agent excreted via glomerular filtration; its elimination from plasma is used as an indirect measure of GFR. Iohexol plasma clearance is performed by injecting 2-10mls of iohexol intravenously. After 6-24 hours (depending on the estimated GFR) a blood sample is drawn and iohexol concentration is measured using high performance liquid chromatography (HPLC). mGFR is then calculated using a formula based on the individual's age, sex and distribution volume. It performs well in comparison with inulin clearance(13). The iohexol mGFR protocols used in Swedish clinics differ only slightly and the national quality assurance programme was operating during the study period(14). A description of iohexol plasma clearance calculation is given in supplementary material.

Swedish laboratories analysed serum creatinine using an enzymatic method or corrected Jaffe method, which are isotope dilution mass spectrometry traceable. Performance as assessed by the Swedish Clinical Chemistry Association was acceptable(15). eGFR was calculated using the CKD-EPI$_{creatinine}$ formulae(16).

Urinary urea and creatinine measurements were reported using the absolute value (ml/min) while mGFR and eGFR were reported with a correction for body surface area (BSA) of 1.73m^2, reflecting routine clinical care. However for the analyses, the urinary clearance measures were corrected for BSA of 1.73m^2 to allow a fair comparison with mGFR/eGFR.

Statistical analysis

Statistical analyses were undertaken using SPSS for Mac version 21 (IBM). Descriptive statistics are presented as mean ± standard deviation or median (interquartile range). Between group differences were assessed according to the data distribution. Multiple imputation was performed for variables when <10% data missing, with 20 imputations, and pooled results used, unless otherwise specified.

The cohort was divided into tertiles according to the clearance marker (ie tertiles of iohexol mGFR, eGFR, Creat-Cl [all adjusted for BSA of 1.73m^2]), and Kaplan Meier unadjusted survival plots were constructed comparing outcome for the clearance markers, by tertile. Cox proportional hazard survival models were constructed for all-cause mortality. Potential confounders were identified from direct acyclic graphs (DAG; dagitty.net) and the assumptions of conditional independence in the DAG were confirmed using linear regression. Co-variates were included in order to assess the effects of the predictor on mortality. The DAG used to produce the models is provided in the Supplementary material (Figure S1). The proportional hazards assumption was tested for each continuous variable by plotting Schoenfeld residuals against time, using loess smoothing. Log minus log plots were used for categorical variables. The proportional hazards assumption was tested by creating time-dependant co-variates for each variable, assessing for interaction and were included in the model as a time-dependant co-variate if the interaction was significant.

Model 1 included age and gender as co-variates. Model 2 (see DAG in Figure S1) was adjusted for: age, gender, Charlson Score, PRD, body mass index (BMI) and serum albumin. Model 3 (see DAG in Figure S1), included Model 2 co-variates plus pulse pressure, haemoglobin and commencement of RRT (time-varying co-variate). Each of the predictors was added to the model *in turn*; iohexol mGFR, eGFR, Creat-Cl, Urea-Cl, Urea-Creat-Cl (all adjusted for BSA of 1.73m^2). The adjusted hazard ratios (aHR) presented are for a one-unit rise in the predictor variable. However Creat-Cl is generally higher than eGFR and Urea-Cl is generally lower, introducing potential bias. Therefore sensitivity analyses were performed; each predictor was log-transformed (not normally distributed) and then standardised for fair comparison. For these analyses, the hazard ratios are per one standard deviation on a logarithmic scale. eGFR CKD-EPI$_{creat}$ was used since it is recommended by KDIGO and performed well in comparison to iohexol mGFR in a cross-sectional analysis of the SRR-CKD(2, 4). Sensitivity analyses were also performed comparing the performance of the urinary clearance markers without correction for BSA.

Several methods are used to estimate the predictive performance of a model. The diagnostic performance is studied through discrimination, separating those diagnosed with the event from those not experiencing it. In this context, good discrimination means that low GFR always produce higher predicted risk than high GFR. In our study, model discrimination was assessed using C-statistics derived by two methods. Multivariate logistic regression models for 2-yr all-cause mortality were built using each predictor in turn with the covariates from the Cox model 3 (using data from the 20th imputation). The C-statistics were calculated by constructing Receiver Operator Characteristic (ROC) curves using the predicted probability from the logistic regression model. Differences between the area under the curve (AUC) of ROC curves was assessed using Hanley and McNeill's method(17). In addition, Harrell's C was calculated for each clearance measure using the output from the adjusted Cox survival model, utilising the total follow-up time available (using Model 3 and data from 20th imputation)(18). These models were built in order to compare the performance of the different measures of renal function, and not for clinical use as a predictor of prognosis.

Calibration assesses the agreement between the observed and the predicted risk by the model. Calibration was assessed using the Hosmer-Lemeshow test; a non-significant p value suggests model calibration (ie no significant difference in proportion of participants predicted versus observed to die). Integrated Discrimination Improvement (IDI) compared the performance of mGFR or urinary clearance measures versus eGFR (as reference) to predict all-cause mortality. The same multivariate model was used as for discrimination. IDI measures the proportion correctly re-classified to a higher or lower risk with the addition of the new biomarker. It is superior to net reclassification index as it incorporates direction and magnitude of risk reclassification, and does not rely on a selected threshold(19).

Results

The cohort included 2,705 patients, 1517 with an iohexol mGFR and eGFR performed contemporaneously and 1,188 with a urinary clearance and eGFR measured contemporaneously; see the flowchart of population and exclusions (Figure 1). Background data are shown in Table 1, except data regarding race (illegal to record in Sweden). Patients were followed for a median of 45 months (interquartile range [IQR] 26-59).

Scatterplots demonstrating the relationship between the measures of GFR are shown in Supplementary Figure S2.

Outcomes

There were 968 deaths during follow-up (35.8% of the total cohort). For those who died during follow-up, median time to death from baseline was 23 months (IQR 11–39). RRT was commenced in 1087 patients (40.2%). There were 621 deaths (23.0%) without starting RRT and 347 patients (12.8%) died after starting RRT. Subsequent mortality analyses include all deaths (with or without RRT initiation). See Figure 1 for details of the mGFR and urinary clearance subgroups.

Aetiological models

mGFR versus eGFR to predict mortality

Kaplan Meier plots of unadjusted survival, comparing tertiles of clearance marker are shown in Figure 2. Cox regression analyses comparing iohexol mGFR and eGFR as predictors of all-cause mortality are shown in Table 2 and Figure 3 (unadjusted model) and Supplementary Figure S3 (adjusted model). Given the inverse relationship between GFR and survival, a lower aHR is suggestive of a stronger relationship between the measure of GFR and all-cause mortality. In the fully adjusted model (Model 3 in Table 2) a rise in mGFR of 1ml/min/1.73m^2 was associated with a 5.3% lower all-cause mortality compared with 1.7% lower for the corresponding change in eGFR (aHR 0.947 [95%CI 0.930–0.964] versus aHR 0.983 [95%CI 0.970–0.996]). In the sensitivity analyses, the relationship is maintained with a 1-SD rise in mGFR (on a logarithmic scale) being associated with a 29.1% lower mortality (aHR 0.701 [95%CI 0.633–0.793]) versus only 8.7% lower for eGFR (aHR 0.913 [95%CI 0.821–1.016]).

Urinary clearance versus eGFR to predict mortality

Cox regression analyses comparing urinary clearance measures and eGFR as predictors of all-cause mortality were performed. Multiple measures of urinary clearance were available in different sub-groups (see Figure 1). Multiple comparisons were only made when all measures were available contemporaneously in a sub-group.

Creat-Cl was measured in 1076 participants and the comparison with eGFR is shown in Table 3, Figures 2&3 (unadjusted model) and Supplementary Figure S3 (adjusted model). Urea-Creat-Cl was measured in 527 participants and the comparisons with Creat-Cl, Urea-Cl and eGFR are shown in Table 4, Figures 2&3 (unadjusted model) and Supplementary Figure S3 (adjusted model).

Urinary Creat-Cl vs eGFR

In the fully adjusted Cox model (Model 3, Table 3), a rise in Creat-Cl of 1ml/min (per 1.73m^2) was associated with 2.3% lower all-cause mortality compared with 1.7% lower for the corresponding change in eGFR (per 1.73m^2) (aHR 0.977 [95%CI 0.967–0.988] versus aHR 0.983 [95%CI 0.969–0.998]). In the sensitivity analyses, the relationship between the performances of the filtration markers change; a 1-SD rise in Creat-Cl (on a logarithmic scale) was associated with 23.9% lower mortality (aHR 0.761 [95%CI 0.686–0.846]) versus only 9.3% lower for eGFR (aHR 0.907, [95%CI 0.812–1.013]).

Urinary Urea-Cl

For Urea-Cl versus eGFR the mortality is 4.6% versus 0.9% lower (aHR 0.954 [0.931–0.978] and 0.991 [0.971–1.011] respectively) in the fully-adjusted model (Model 3, Table 4). In the sensitivity analyses, a markedly altered relationship is observed, with a 1-SD rise in Urea-Cl (logarithmic scale) associated with 29.1% lower mortality versus 3.1% (aHR 0.709 [0.607–0.829] and 0.969 [0.833–1.128] respectively), in the fully adjusted model.

Urinary Urea-Creat-Cl

For Urea-Creat-Cl versus eGFR, mortality was 3.1% versus 0.9% lower (aHR 0.969 [0.950–0.988] and 0.991 [0.971–1.011] respectively) in the fully-adjusted model (Model 3, Table 4). In the sensitivity analyses, an altered relationship is again observed, with a 1-SD rise in Urea-Creat-Cl (on a logarithmic scale) associated with 25.5% lower mortality versus 3.1% (aHR 0.745 [0.639–0.868] and 0.969 [0.833–1.128] respectively), again when the model was fully adjusted for co-variates.

Therefore, within the sub-group with multiple urine clearance measures, the Urea-Cl had the strongest relationship with all-cause mortality. Sensitivity analyses were also performed for the urinary clearance markers without adjustment for BSA, (shown in Supplementary Tables S1 and S2) and the relative performance of the clearance markers was unchanged.

Prognostic Models

Discrimination and Calibration

Model discrimination for mGFR, Creat-Cl and Urea-Creat-Cl, compared to eGFR are shown in Figure 4 (and supplementary Table S3). The C-statistic (from the 2-yr logistic regression model) was significantly higher for mGFR than eGFR demonstrating superior discrimination, using Hanley and McNeill's method of comparing the AUC of ROC curves.(17) The parameter estimates for variables in the logistic regression models are shown in Table S4. In the urinary clearance groups the differences were not significant. Using Harrell's C, the relative discriminative performance of the clearance measures was the same as the logistic regression method, except for mGFR and eGFR where no clear difference was seen between the two measures. All the models were well calibrated using Hosmer-Lemeshow goodness of fit test (no significant differences between the expected and observed proportion who died) (supplementary Table S3).

Integrated Discrimination Improvement

IDI was used to assess improvement in the prognostic model with mGFR or urinary clearance measures in place of eGFR. The results are shown in supplementary Table S4. Replacing eGFR with mGFR resulted in a improvement in the IDI (overall IDI 0.023). However, replacement of eGFR with Creat-Cl, Urea-Cl or Urea-Creat-Cl did not result in a significant change in the IDI.

Discussion

We have shown that mGFR (iohexol plasma clearance) is a superior predictor of all-cause mortality than eGFR in a Swedish Registry population of patients with CKD. However the demonstration of a stronger relationship does not necessarily mean that the predictor has a superior influence on prognosis. Therefore both aetiological models (to demonstrate the strength of the relationship) and prognostic models (to compare the contribution of the respective markers to prognostication) are needed, as performed here. In our models we show that the measured GFR is consistently superior across the aetiological Cox models (adjusted and unadjusted), demonstrating the importance of GFR itself as a predictor of adverse outcome over the additional non-GFR determinants of outcome associated with creatinine-derived eGFR. Prognostic models were built to allow comparison of the performance of the markers, and have not been validated for clinical use to estimate prognosis. Measured GFR was also generally superior to eGFR in the prognostic models (discrimination using 2-yr logistic regression model, calibration and IDI, but discriminative performance of mGFR and eGFR was similar using Harrell's C).

However, the relative performance of mGFR in the prognostic models was weaker than the aetiological models. Creatinine-based eGFR using the CKD-EPI formulae performed well in the prognostic model, and while mGFR was superior, the difference was modest (at best) and may not be clinically relevant.

In a separate sub-group, urinary clearance measures were performed. There were significant differences in the baseline characteristics between the iohexol mGFR group and the urinary clearance group therefore direct comparisons between mGFR and urinary clearance cannot be made. However comparisons can be made between different urinary clearance measures performed in the same patients. Supplementary Figure S2 demonstrates the relationship between Creat-Cl, Urea-Cl and combined Urea-Creat-Cl versus eGFR respectively in the cohort. Creat-Cl is generally higher than eGFR for a given patient due to a relative increase in tubular secretion of creatinine in advanced CKD (median Cr Cl 23ml/min), Urea-Cl is lower due to tubular re-absorption (median Ur Cl 14ml/min), and the combined Urea-Creat-Cl is closest to eGFR in the cohort (18ml/min and 20ml/min/1.73m^2 respectively). Urinary clearance measures showed less consistent performance than mGFR across the aetiological and prognostic models. Given the systematic differences in measurement of the filtration markers observed above, (e.g. Creat-Cl being consistently higher than Urea-Cl at a given level), the sensitivity analyses aided interpretation (using log transformation and standardisation to remove these differences). Each urinary filtration marker showed a strong independent relationship with all-cause mortality in the aetiological models, similar in magnitude to each other and stronger than eGFR. However, while they showed good discrimination, this was not significantly superior to eGFR. The models were well calibrated, but again, using the IDI, were not superior to eGFR. The strongest performer among the urinary markers was Urea-Cl.

Iohexol plasma clearance performs well compared with inulin clearance, the historic gold standard GFR measure(13). It is considered to be more accurate than eGFR as it is closer to “true GFR”. Worsening kidney disease is associated strongly with increased all-cause mortality(1, 20). However eGFR equations were developed to estimate GFR, not for prognostication (though GFR itself is a strong predictor of prognosis). However it does not necessarily follow that iohexol mGFR is a superior predictor of all-cause mortality, as mGFR does not take account of non-GFR determinants of outcome such as protein-energy wasting, low muscle mass and reduced creatinine generation. In a post-hoc analysis of the MDRD study, Tangri et al demonstrated that, after adjusting for GFR in their multi-variate model, a higher creatinine remained independently associated with lower mortality, demonstrating the role of the non-GFR determinants of creatinine(21). Conversely, low spot urine creatinine concentration is independently associated with mortality(22). Other work demonstrated an association between creatinine and non-traditional cardiovascular risk factors, independent of GFR(23). However in this study we have demonstrated the superior performance of mGFR over eGFR in the aetiological Cox models. A previous SRR-CKD study showed that the CKD-EPI$_{creat}$ formulae overestimate GFR in advanced kidney disease(4). Our findings suggest that the superior accuracy of mGFR (and the independent relationship between GFR and all-cause mortality) outweighs the aetiological effects of the non-GFR determinants of outcome as measured by creatinine.

The lack of superiority shown for formal urinary measures over eGFR (especially Creat-Cl and Urea-Creat-Cl) may be because these measures reflect the same creatinine based non-GFR determinants of outcome as eGFR, or simply due to inaccuracies in the urine collections. Urea-Cl performed well to predict all-cause mortality. While it is inferior for measuring GFR alone (40-50% of filtered urea may be reabsorbed in the tubules), higher urea generation may reflect high protein content in the diet(3). Therefore this may be a marker of good patient outcome. The lack of a significant difference in discrimination and IDI for urinary measures over eGFR may simply reflect lack of statistical power (though discrimination models were consistent between the Creat-Cl group [n=1076] and the Urea-Creat-Cl group [n=527]).

Calculating eGFR from a blood sample is undoubtedly the most convenient GFR assessment for patient, clinician and laboratory, not to mention cost effectiveness, and must be advocated for widespread use to identify those with CKD(24). Since eGFR reporting was introduced, timed urine collection use has fallen dramatically in many countries, although is still advocated by some for patients with advanced CKD(25). However clinical practice differs between countries and we have exploited the ongoing practice of formal measures in Sweden for this study. In advanced CKD, where accurate measures of GFR will aid decision-making regarding timing of RRT, vascular access formation, or drug dosing, and the eGFR formulae are least accurate, clear benefits of a formal measure of GFR are seen. We have demonstrated the strong aetiological relationship with mortality which may aid prognostication in patients with advanced CKD.

The strengths of this study lie in the inclusive, representative nature of the cohort, the large numbers undergoing mGFR testing and the complete follow-up of patients using linked national Swedish Registries. However, there are also limitations. As the study utilises routinely collected data, participants had the formal measure of GFR of their nephrologist's choice, which could introduce confounding by indication. Only a sub-set had multiple contemporaneous measures, limiting direct comparisons. While data regarding date of death were complete, data regarding the cause of death were not which limited the analyses to all-cause mortality only. Ethnicity data were not recorded due to Swedish regulations. However the proportion of people from minority ethnic groups is low in Sweden and the findings will reflect the majority white population. These findings therefore may not translate to other ethnic groups. Data regarding smoking status and albuminuria were incomplete so these variables could not be included in the models. We did not have additional endogenous measures of kidney function such as cystatin C or beta trace protein to compare with the exogenous measures. Lastly iohexol mGFR is itself only an estimate of true GFR (which cannot be directly measured) and we used only a single time-point so we were unable to investigate the influence of GFR slope on outcomes, as has been done elsewhere(26).

These findings should be confirmed in a prospective cohort to exclude residual confounding or selection bias. Obtaining urinary measures, endogenous measures of eGFR and mGFR contemporaneously would allow direct comparisons.

In conclusion, in aetiological and prognostic models, mGFR was superior to eGFR in predicting mortality in adults with CKD stage 4/5 attending Swedish nephrology clinics. This demonstrates the strong etiological role of GFR to predict adverse outcome versus the additional non-GFR determinants of outcome associated with creatinine-based eGFR. The relatively modest predictive enhancement suggests that eGFR may be sufficient to use in most scenarios in everyday clinical practice, while mGFR adds prognostic information when eGFR is believed or suspected to be biased.

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Tables

Table 1 Baseline demographics for a cohort of 2705 patients with multiple contemporaneous measurements of kidney function.

Variable	Total cohort n=2705	Missing data for total cohort	Iohexol sub-group n=1517	Urinary clearance sub-group n=1194	Difference between sub-groups
Age (years)	70 (60 - 79) (range 18-99)	0%	72 (61 - 79)	69 (59 - 78)	p=0.001
Gender (% male)	66%	0%	65%	69%	p=0.041
Primary Renal Disease					
Primary glomerulonephritis	10.8%	0%	6.9%	15.7%	p<0.001
Interstitial disease	9.3%		8.0%	11.0%	
Hypertension/renovascular	24.1%		24.7%	23.3%	
Diabetic nephropathy	23.9%		22.5%	25.5%	
Other	10.9%		11.5%	10.2%	
CKD; aetiology unknown	21.0%		26.4%	14.3%	
Centre					
Local Hospital	19.0%	0%	26.9%	8.8%	p<0.001
Regional Hospital	19.0%		24.1%	12.4%	
University Hospital	62.1%		49.0%	78.8%	
Diabetes mellitus	36.8%	0.6%	36.9%	36.7%	0.732
Antihypertensive medication* (number)	3 (2 – 4)	0%	3 (2 – 4)	3 (2 – 4)	p=0.004
Protein restricted diet	9%	0%	8.7%	9.4%	p=0.513
Weight (kg)	79.8 (±17.4)	2.2%	79.8 (±17.7)	79.8 (±17.0)	p=0.498
Height (m)	1.71 (±0.1)	7.4%	1.70 (±0.1)	1.72 (±0.1)	p=0.001
Body mass index (kg/m^2)	27.3 (±5.5)	7.9%	27.5 (±5.7)	27.0 (±5.0)	p=0.044
Body Surface Area (m^2)	1.91 (±0.23)	7.9%	1.91 (±0.22)	1.92 (±0.23)	p=0.172
Mean arterial blood pressure (mmHg)	99 (±14)	2.9%	98 (±13)	100 (±14)	p<0.001

Pulse pressure (mmHg)	64 (±20)	2.9%	63 (±19)	65 (±20)	p=0.058
Weighted Charlson score	3 (2 – 4)	0%	3 (2 – 4)	3 (2 – 4)	p=0.103
Serum creatinine (mg/dL) **(µmol/L)**	2.8 (2.3 – 3.8) 251 (204–340)	0%	2.8 (2.3 – 3.7) 250 (196–330)	2.9 (2.4 – 4.0) 253 (210–354)	p=0.528
eGFR (mL/min/1.73m^2) (CKD-EPI)	20 (14 – 26)	0%	20 (14 – 27)	20 (13 – 26)	p=0.830
mGFR (mL/min/1.73m^2)	-	0% of mGFR group	18 (13 – 23)	-	-
24-hour creatinine clearance	-	94% of urine cl group	-	23 (15 - 31)	-
24-hour urea clearance	-	46% of urine cl group	-	14 (9 – 19)	-
24-hour urea-creatinine clearance	-	56% of urine cl group	-	18 (12 – 24)	-
24-hour urine albumin (mg/day)	532 (119-1896)	20.7%	667 (106–2396)	523 (119–1753)	p=0.891
Albumin: creatinine ratio (mg/mmol)	37 (7 – 154)	80.9%	30 (5 – 127)	59 (11 – 206)	p=0.011
Haemoglobin (g/L)	121 (±15)	3.0%	121 (±15)	121 (±15)	p=0.382
Albumin (g/L)	36 (±4)	3.5%	36 (±4)	37 (±4)	p=0.006
Phosphate (mmol/L)	1.37 (±0.35)	5.6%	1.36 (±0.35)	1.37 (±0.36)	p=0.273

Presented as median (interquartile range) or mean (±SD) unless otherwise stated. Data presented are for complete dataset, pre-imputation. Difference between groups was assessed using independent samples t test, Mann-Whitney U test or chi-square test as appropriate.

*Antihypertensive medication includes diuretics

Table 2 Cox Proportional Hazards Model for all cause mortality comparing mGFR (using iohexol plasma clearance) and eGFR CKD-EPI (creatinine) in 1517 patients with contemporaneous measures.

n=1517	**Univariate**	**Multivariate Model 1***	**Multivariate Model 2#**	**Multivariate Model 3§**
mGFR (ml/min/1.73m²)	0.925 (0.910 – 0.940) p<0.001	0.930 (0.914 – 0.945) p<0.001	0.932 (0.917 – 0.948) p<0.001	0.947 (0.930 – 0.964) p<0.001
eGFR (ml/min/1.73m²)	0.966 (0.955 – 0.977) p<0.001	0.965 (0.954 – 0.977) p<0.001	0.965 (0.954 – 0.977) p<0.001	0.983 (0.970 – 0.996) p=0.009
Standardised values on a logarithmic scale				
Log mGFR (per 1 SD)	0.607 (0.551 – 0.669) p<0.001	0.624 (0.564 – 0.690) p<0.001	0.638 (0.577 – 0.706) p<0.001	0.709 (0.633 – 0.793) p<0.001
Log eGFR (per 1 SD)	0.783 (0.716 – 0.855) p<0.001	0.776 (0.709 – 0.849) p<0.001	0.778 (0.710 – 0.853) p<0.001	0.913 (0.821 – 1.016) p=0.095

mGFR; measured Glomerular Filtration Rate, eGFR; estimated Glomerular Filtration Rate, 1SD; 1 standard deviation

***Model 1** co-variates; age, sex; #**Model 2** co-variates; age, sex, Charlson Score, Primary Renal Diagnosis, BMI, serum albumin; §**Model 3** co-variates; age, sex, pulse pressure, Charlson Score, Primary Renal Diagnosis, BMI, serum albumin, Haemoglobin, commencement of RRT (modelled as a time-varying covariate)

For each measure of kidney function (the predictor), the unadjusted hazard ratio is shown, followed by 3 models with co-variates, as described above (95% confidence intervals in brackets). The predictor variables were not normally distributed, therefore they were converted to a logarithmic scale. Then, in order to facilitate direct comparison the predictor variables were standardized (mean of zero and standard deviation of 1). In summary, the hazard ratios are described for the crude measure of the predictor and then per 1SD rise on a logarithmic scale.

Table 3 Cox Proportional Hazards Model for all cause mortality comparing 24-h creatinine clearance, corrected for body surface area (BSA) of 1.73m^2 and eGFR CKD-EPI (creatinine) (also corrected for BSA) in 1076 patients with contemporaneous measures.

n=1076	**Univariate**	**Multivariate Model 1***	**Multivariate Model 2#**	**Multivariate Model 3§**
Creat Clearance (ml/min/1.73m^2)	0.956 (0.946 – 0.966) p<0.001	0.964 (0.953 – 0.974) p<0.001	0.966 (0.956 – 0.977) p<0.001	0.978 (0.966 – 0.990) p<0.001
eGFR (ml/min/1.73m^2)	0.965 (0.954 – 0.977) p<0.001	0.967 (0.955 – 0.979) p<0.001	0.965 (0.953 – 0.977) p<0.001	0.983 (0.969 – 0.998) p=0.025
Standardised values on logarithmic scale (using values corrected for BSA)				
Log Creat Clearance (per 1 SD)	0.648 (0.593 – 0.708) p<0.001	0.687 (0.627 – 0.754) p<0.001	0.705 (0.642 – 0.774) p<0.001	0.777 (0.698 – 0.863) p<0.001
Log eGFR (per 1 SD)	0.784 (0.721 – 0.854) p<0.001	0.786 (0.718 – 0.860) p<0.001	0.779 (0.710 – 0.854) p<0.001	0.907 (0.812 – 1.013) p=0.084

eGFR; estimated Glomerular Filtration Rate, Creat; creatinine, 1SD; 1 standard deviation

***Model 1** co-variates; age, sex; #**Model 2** co-variates; age, sex, Charlson Score, Primary Renal Diagnosis, BMI, serum albumin; §**Model 3** co-variates; age, sex, pulse pressure, Charlson Score, Primary Renal Diagnosis, BMI, serum albumin, Haemoglobin, commencement of RRT (modelled as a time-varying covariate)

For each measure of kidney function (the predictor), the unadjusted hazard ratio is shown, followed by 3 models with co-variates, as described above (95% confidence intervals in brackets). The predictor variables were not normally distributed, therefore they were converted to a logarithmic scale. Then, in order to facilitate direct comparison the predictor variables were standardized (mean of zero and standard deviation of 1). In summary, the hazard ratios are described for the crude measure of the predictor (corrected for body surface area) and then per 1SD rise on a logarithmic scale.

Table 4 Sensitivity analysis of Cox Proportional Hazards Model for all cause mortality comparing 24-h urea-creatinine clearance, 24-h urea clearance, 24-h creatinine clearance corrected for body surface area (BSA) of 1.73m^2, and eGFR CKD-EPI$_{creat}$ (already corrected for BSA) in 527 patients with contemporaneous measures.

n=527	**Univariate**	**Multivariate Model 1***	**Multivariate Model 2#**	**Multivariate Model 3§**
Urea-Creat Clearance (ml/min/1.73m^2)	0.943 (0.926 – 0.961) p<0.001	0.957 (0.939 – 0.976) p<0.001	0.959 (0.941 – 0.978) P<0.001	0.970 (0.948 – 0.992) P=0.007
Urea Clearance (ml/min/1.73m^2)	0.920 (0.898 – 0.942) p<0.001	0.938 (0.915 – 0.963) p<0.001	0.941 (0.917 – 0.965) p<0.001	0.951 (0.925 – 0.978) p<0.001
Creat Clearance (ml/min/1.73m^2)	0.962 (0.949 – 0.975) p<0.001	0.972* (0.958 – 0.987) p<0.001	0.974 (0.959 – 0.988) p<0.001	0.984 (0.967 – 1.001) p=0.058
eGFR CKD-EPI (ml/min/1.73m^2)	0.972 (0.957 – 0.986) p<0.001	0.975 (0.960 – 0.991) p<0.001	0.974 (0.959 – 0.990) p=0.002	0.991 (0.971 – 1.011) p=0.379
Standardised values on logarithmic scale				
Log Urea-Creat Clearance (per 1 SD)	0.640 (0.567 – 0.723) p<0.001	0.693 (0.608 – 0.790) p<0.001	0.711 (0.624 – 0.810) p<0.001	0.757 (0.648 – 0.884) p<0.001
Log Urea Clearance (per 1 SD)	0.617 (0.543 – 0.700) p<0.001	0.680 (0.593 - 0.780) p<0.001	0.693 (0.603 – 0.796) p<0.001	0.737 (0.631 – 0.860) p<0.001
Log Creat Clearance (per 1SD)	0.678 (0.604 – 0.761) p<0.001	0.724 (0.641 – 0.818) p<0.001	0.742 (0.656 – 0.838) p<0.001	0.792 (0.684 – 0.919) p=0.002
Log eGFR CKD-EPI (per 1 SD)	0.827 (0.744 – 0.920) p<0.001	0.843 (0.752 – 0.945) p<0.001	0.841 (0.749 – 0.944) p=0.003	0.969 (0.833 – 1.128) p=0.687

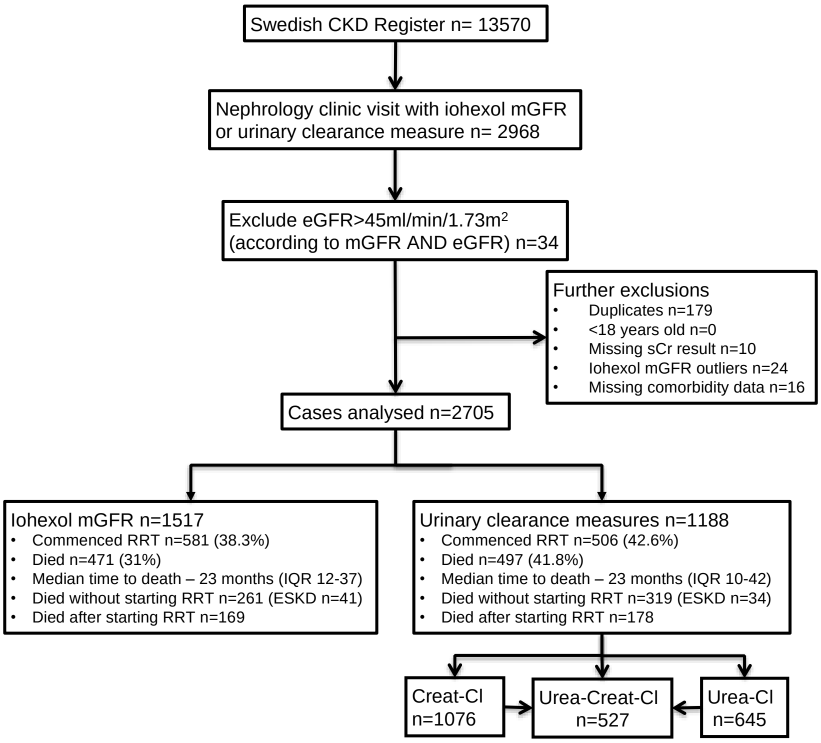
95%CI; 95% confidence interval, eGFR; estimated Glomerular Filtration Rate, Creat; creatinine, 1SD; 1 standard deviation

***Model 1** co-variates; age, sex; **#Model 2** co-variates; age, sex, Charlson Score, Primary Renal Diagnosis, BMI, serum albumin; **§Model 3** co-variates; age, sex, pulse pressure, Charlson Score, Primary Renal Diagnosis, BMI, serum albumin, Haemoglobin, commencement of RRT (modelled as a time-varying covariate)

For each measure of kidney function (the predictor), the unadjusted hazard ratio is shown, followed by 3 models with co-variates, as described above. The predictor variables were not normally distributed, therefore they were converted to a logarithmic scale. Then, in order to facilitate direct comparison the predictor variables were standardized (mean of zero and standard deviation of 1). In summary, the hazard ratios are described for the crude measure of the predictor and then per 1SD rise on a logarithmic scale.

Figures

Figure 1 Flowchart of population and exclusions



mGFR; measured Glomerular Filtration Rate, eGFR; estimated Glomerular Filtration Rate, sCr; serum creatinine, Creat Cl; creatinine clearance, Urea-Creat Cl; urea-creatinine clearance, Urea Cl; urea clearance

Figure 2 Kaplan Meier survival plots comparing (a) mGFR versus eGFR and (b) creatinine clearance versus eGFR. Patients were divided into tertiles according to kidney function defined by each test

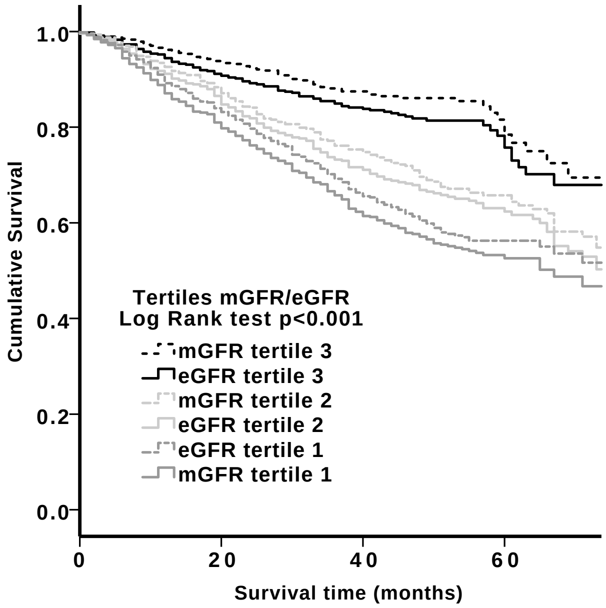


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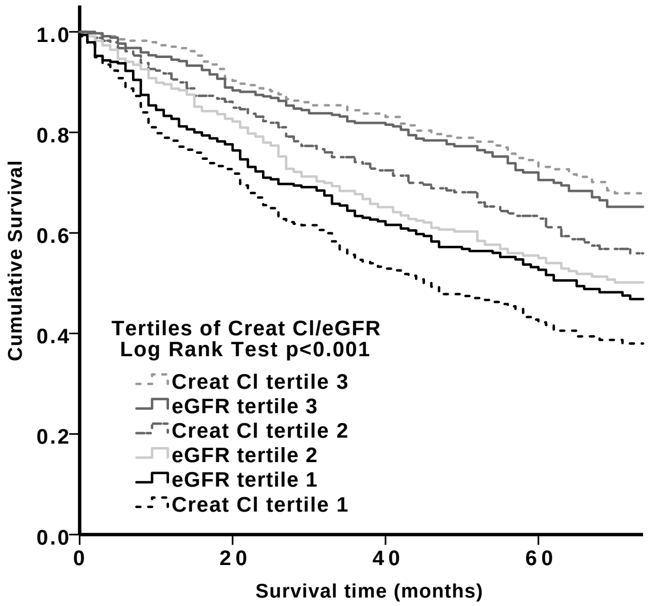
Figure 2b



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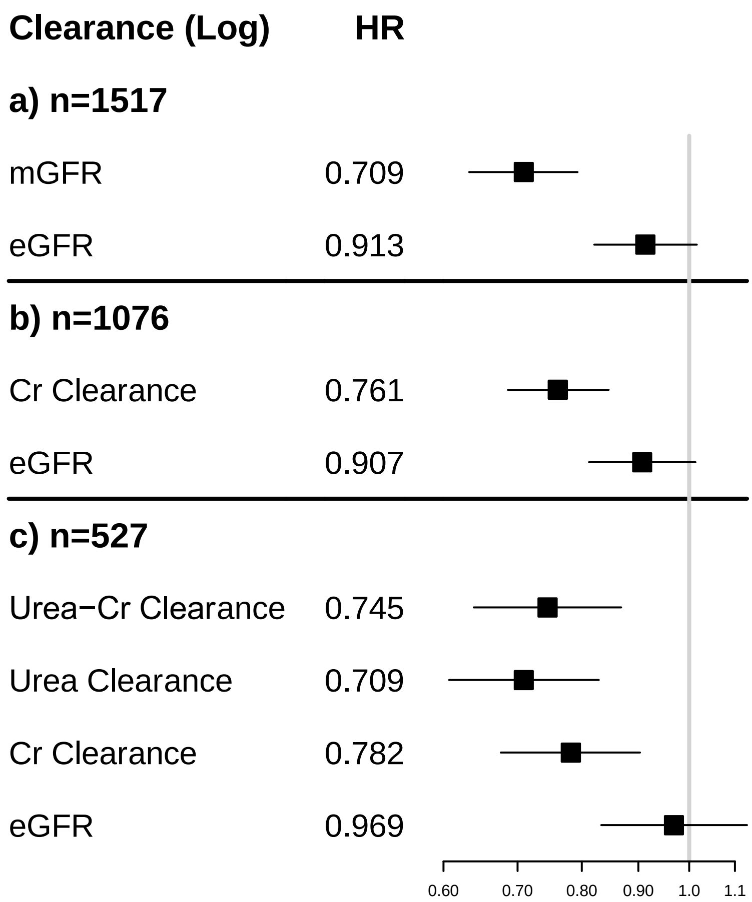
mGFR; measured Glomerular Filtration Rate, eGFR; estimated Glomerular Filtration Rate, Creat Cl; creatinine clearance

Figure 3 Forest plots of unadjusted hazard ratios for all cause mortality comparing (a) mGFR and eGFR, in 1517 patients with contemporaneous measures (b) 24-h creatinine clearance (ml/min/1.73m^2) and eGFR in 1076 patients with contemporaneous measures and (c) 24-h urea-creatinine clearance, 24-h urea clearance, 24-h creatinine clearance (all ml/min/1.73m^2) and eGFR in 527 patients with contemporaneous measures



Please note the sub-groups contain different individuals and hazard ratios can only be compared within the sub-group not across sub-groups ie comparison of mGFR with urea clearance is not valid

Figure 4 Discrimination models for 2 year all cause mortality comparing (a) mGFR (iohexol plasma clearance) with eGFR (CKD-EPI), (b) 24-h creatinine clearance with eGFR (CKD-EPI) and (c) 24-h urea-creatinine clearance with eGFR (CKD-EPI)

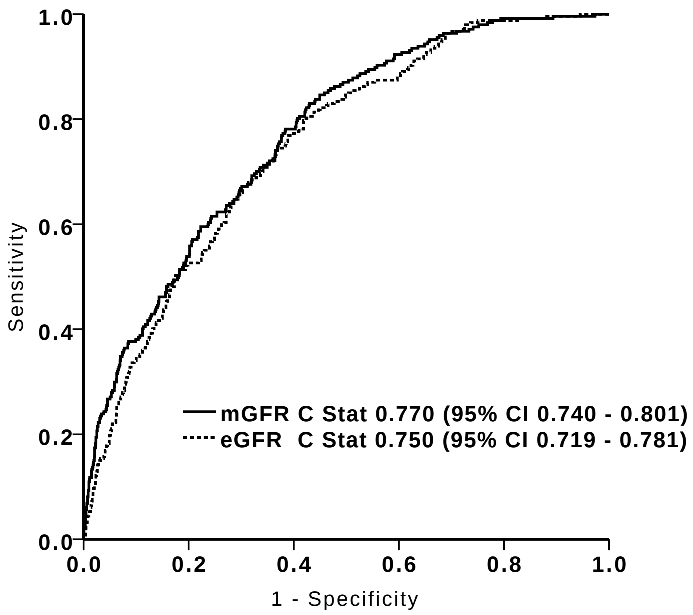


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Figure 4b

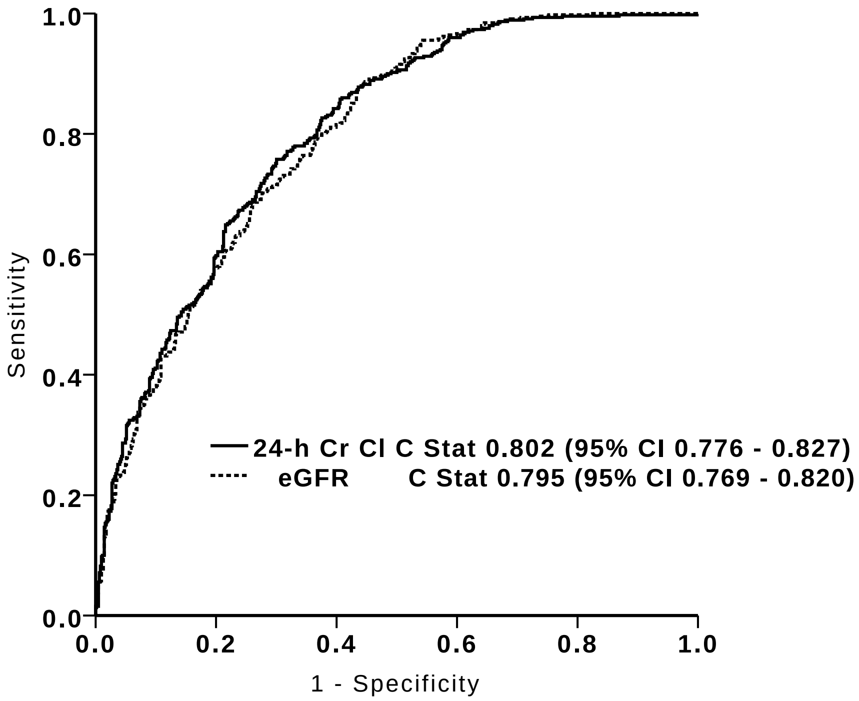

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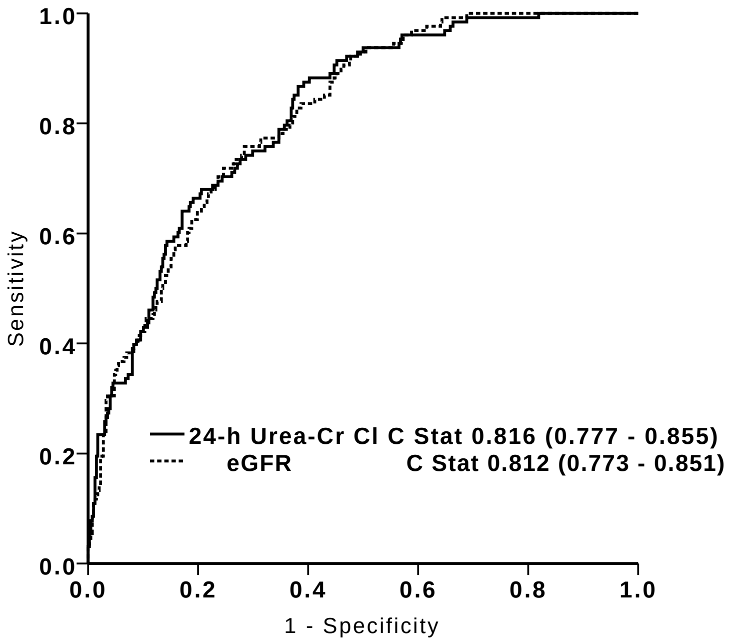
Figure 4c



Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
24-h Urea-Cr Cl C Stat 0.816 (0.777 - 0.855)
eGFR C Stat 0.812 (0.773 - 0.851)